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10/748,112	12/29/2003	Sanjay D. Khare	06843.0052-00000	1751

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,112	KHARE, SANJAY D.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-31,47-62,77-86,104-134 and 153-159* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104,110,113 and 116-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/19/04;08/16/05;05/22/06;11/05/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 16-31,47-62,77-86,105-109,111,112,114,115,122-134 and 153-159.

DETAILED ACTION

1. Applicant's remarks, filed on 11/05/2007, are acknowledged.

Claims 16-31, 47-62, 77-86, 104-134, and 153-159 are pending.

Claims 16-31, 47-62, 77-86, 105-109, 111-112, 122-134, and 153-159 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Inventions/Species, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 12/26/2006.

2. Applicant's election with traverse of Group I, drawn to a method for treating rheumatoid arthritis by administering an AGP3 inhibitor and a TNF-α inhibitor selected from at least one of etanercept, infliximab, and D2E7), in the reply filed on 11/05/2007 is acknowledged.

The traversal is on the grounds that the restriction requirement allegedly limits the scope of Applicant's claims.

This is not found persuasive, because, as set forth at page 6 of the restriction requirement of 07/05/2007 claims 104, 110, and 119 – 121 have been identified as the linking claims.

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species wherein the TNF-α inhibitor is etanercept is acknowledged.

Claims 114 and 115 are withdrawn from further consideration by the Examiner, under 37 C.F.R. § 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Claims 104, 110, 113, and 116 – 121 are presently under consideration.

3. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP §608.01(o). Correction of the following is required:

Applicant is requested to identify the written support for claim 110, particularly the claimed limitations of "infliximab." Alternatively, Applicant is invited to amend the specification to provide antecedent basis for the claimed subject matter.

4. Claim 110 is objected to because of the following informalities: an apparent spelling error in the word "infliximab." Appropriate correction is required.

Claims 113 and 116 – 118 are objected to as being dependent on a non-elected claim. It is suggested that Applicant rewrite the claims in independent form to include the limitations of base claims.

5. The following is a quotation of the **first paragraph of 35 U.S.C. 112**:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 104, 110, 113, and 116 – 121 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

A. Applicant is not in possession of the claimed method, because applicant is not in possession of the generically recited "AGP3 inhibitor," including the generically recited "peptide inhibitor of AGP3" or "AGP3 peptibody," or the generically recited "TNF-α inhibitor."

Applicant has disclosed a limited number of species, i.e. an AGP3 peptibody of SEQ ID NO:1 (e.g. Figure 19) and anti-BlyS antibodies (e.g. paragraph 0264 at pages 94 – 95), and TNF-α inhibitors based on TNF receptors and antibodies (e.g. paragraph 0226 at page 81). In the absence of a disclosure of sufficiently detailed, relevant identifying characteristics, such as complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics, the skilled artisan cannot envision all the contemplated AGP3 and TNF-α inhibitors encompassed by the instant claims.

A person of skill in the art envision the generically recited "inhibitors" encompassed by the scope of the claims as presently recited, because it was well

known in the art at the time the invention was made that molecules having highly diverse structural and functional properties can function as "inhibitors." For example, Huang (Pharmacology and Therapeutics, 2000, 86: 201 – 215; see entire document) reviews e.g. on page 202 the daunting task faced by the skilled artisan in developing small molecule regulators of protein function, and notes that the process requires long periods of trial and error testing. The structure of such molecules cannot be readily envisioned by one of skill in the art based upon the written description provided in the specification as-filed.

Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993). The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, §1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

B. Applicant is not in possession of the claimed method, because Applicant is not in possession of "BAFFR."

The specification does not appear to disclose any structural or functional features of BAFFR. The specification discloses in paragraph 0264 that information on BAFFR is available in WO 01/87977; however, the referenced publication does not appear to disclose any structural or functional features of BAFFR. Therefore, Applicant has not provided an adequate written description of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, January 5, 2001.

7. Claims 104, 110, 113, and 116 – 121 are rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

It is noted that the elected invention is drawn to a method of treating rheumatoid arthritis; however, the rejection is set forth with regard to the full scope of the generic claims as presently recited.

The specification does not enable one of skill in the art to make and use the invention as claimed without undue experimentation. Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification does not provide a sufficient enabling description of a method of treating rheumatoid arthritis, or of the generically recited "inflammatory or autoimmune condition."

The specification discloses in Example 5 at pages 135 – 136 that combination therapy using PEG-sTNFR-1 and an AGP3 peptibody reduced arthritic score in collagen-induced arthritis in arthritis-susceptible B10.RIII mice. This is not deemed to be sufficiently predictive of treating human subjects suffering from RA or other inflammatory or autoimmune conditions, for the reasons set forth herein.

One of skill in the art at the time the invention was made was aware that it is unpredictable whether an agent shown to treat CIA would treat arthritis in humans. While the Examiner acknowledges that CIA has been used for a number of years as a model for studying arthritis, the limitations of the CIA model have long been appreciated. For example, in 1986 Stuart et al. (Lab. Invest. 1986; 54(1):1-3) cautioned that there are several reason why the CIA model cannot be unequivocally accepted as an model of rheumatoid arthritis because it is induced, lacks many of the extra-articular manifestations of rheumatoid disease and is generally explosive in onset (see bridging paragraph of pages 1-2). Further, in the instant working example treatment began at the time of clinical onset of the disease (paragraph 0372 at pages 135 – 136). Unlike disease models in which immunization is used to produce disease and the timing of disease initiation is therefore known, human autoimmune diseases are not usually diagnosed until the disease has progressed enough to result in pathology.

Further, since the efficacy of therapeutic antibodies to lymphocyte regulatory molecules can be species- and model-dependent, it is unpredictable whether reliance on the experimental observations in the experimental models described in the instant specification provides the basis for employing the recited antibodies for treating RA, or any autoimmune or inflammatory disease. For example, Blazar et al. (J. Immunol., 1996, 157: 3250 – 3259; see entire document, in particular, e.g. page 3257, column 2 first paragraph) disclose that issues such as tissue distribution, half-life, affinity and avidity obtained with various reagents targeting costimulatory molecules might prove to be highly important in achieving a therapeutic effect. Therefore, any conclusion regarding the efficacy of immune modulation on altering in vivo immune response should be interpreted in light of the specific reagent used (Blazar et al., see page 3257, column 2, paragraph 1). Thus there is insufficient evidence that the animal model used in the experiments disclosed in the specification would be predictive of the therapeutic methods encompassed by the claims.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In view of insufficient guidance by the instant specification and the lack of predictability of the art to which the invention pertains with respect to immune cell regulation, in particular with respect to AGP3 inhibition, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of the clinical protocols, and absent working examples providing evidence that the claimed methods are effective for treating any autoimmune diseases other than the specific experimental conditions in mice described in the instant specification.

8. The following is a quotation of the appropriate paragraphs of **35 U.S.C. 102** that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 104, 110, 113, and 116 – 121 are rejected under **35 U.S.C. 102(a) and 102(e)** as being anticipated by Min et al. (WO 02/092620; of record – cited on IDS of 08/19/2004; see entire document).

Min et al. teach a TALL-1 inhibitory peptibody of SEQ ID NO:123 (e.g. example 2 at pages 66 – 75, more specifically Table 5B at pages 67 – 70), which is identical to the instantly recited SEQ ID NO:1, as evidenced by the attached alignment. TALL-1 is an art-recognized synonym of AGP3, as evidenced e.g. by Min et al. at page 76, lines 8 – 9.

Min et al. further teach methods of using the compounds of the invention for treatment of rheumatoid arthritis (e.g. page 46), in particular in combination with TNF antagonists (inhibitors), such as etanercept or D2E7 (e.g. page 49).

Since the AGP3 inhibitor taught by Min et al. is the same as the instantly recited peptibody of SEQ ID NO:1, it inherently has the same functional properties, such as preventing binding of AGP3 to BAFFR and TACI, as recited in claim 113.

Therefore, the reference teachings anticipate the instant claimed invention.

10. Claims 104, 110, 113, and 116, and 119 – 121 are rejected under **35 U.S.C. 102(b)** as being anticipated by Boyle et al. (WO 01/85782; of record – cited on IDS of 08/19/2004; see entire document).

Boyle et al. teach a protein AGP-3 and its receptor, AGP-3R (e.g. pages 3 – 4, bridging paragraph). AGP-3R of Boyle et al. (Figure 18 and SEQ ID NO:43) appears to be identical to the instantly recited TACI (Figure 37 and SEQ ID NO:27).

Boyle et al. further teach fusion proteins between a fragment of AGP-3R-related sequence which interacts with AGP-3 and an Fc region of an immunoglobulin (e.g. page 21 first full paragraph). One of skill in the art would understand that such fusion protein interacts with AGP-3 and prevents binding of AGP-3 to its receptor, i.e. is an AGP-3 inhibitor. Boyle et al. further teach using such AGP-3R-related proteins for treatment of rheumatoid arthritis (e.g. pages 26 – 27, bridging paragraph), in particular in combination with TNF antagonists such as etanercept and D2E7 (e.g. page 28 lines 19 – 28).

Therefore, the reference teachings anticipate the instant claimed invention.

11. Conclusion: no claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is (571)272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ILIA OUSPENSKI, Ph.D./
Examiner, Art Unit 1644
February 13, 2008